Microbial Keratitis in East Africa: why are the outcomes so poor?

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Abstract:

Purpose

Microbial keratitis (MK) is a major cause of blindness in Africa. This study reports the epidemiology, causative organism, management and outcome of MK in people admitted to a large referral hospital in Northern Tanzania, and explores why the outcomes are so poor for this condition.

Methods

A retrospective review of all admissions for MK during a 27-month period. Information was collected on: demographics, history, examination, microbiology, treatment and outcome.

Results

170 patients with MK were identified. Presentation was often delayed (median 14 days), and more delayed if another health facility was visited first (median 21 days). Appropriate intensive antibiotic treatment was prescribed in 19% before admission. Lesions were often severe (41% >5mm). Filamentary fungi were detected in 25% of all specimens (51% of specimens with a positive result). At discharge 66% of affected eyes had a visual acuity of less than 6/60. Perforations developed in 30% and evisceration was necassary in 8%. Perforation was associated with large lesions and visiting another health facility. HIV infection was diagnosed in 16% of individuals tested, which is approximately twice the prevalence found in the wider population.

Conclusions

Microbial keratitis is a significant clinical problem in this region, which generally has a very poor outcome. Delayed presentation is a critical issue. Fungal keratitis is a prominent cause and there is an indication that HIV may increase susceptibility. Prompt recognition and appropriate treatment in primary / secondary health facilities and rapid referral when needed may reduce the burden of blindness from this disease.

Introduction:

Blinding corneal opacification, excluding trachoma, onchocerciasis and childhood related causes, accounted for 5.1% of global blindness (1.9 million).[1] In East and Central Africa (Afr-E) corneal opacification (excluding these other causes) accounted for 12% of blindness.[1] In addition, many millions more are blind in one eye from corneal pathology, which is most commonly due to either infectious keratitis or trauma. Microbial keratitis (MK) in the developing world has been described as a "silent epidemic".[2] Because of the unilateral nature of MK, the prevalence of its blinding complications and the burden of disability it causes are underreported. It has been estimated that there are 2 million incident cases of monocular blindness each year worldwide.[3] Two studies from the Tropics (none from Africa) have attempted to estimate the population incidence of MK, giving results ranging between 113 and 789/100,000/year.[4, 5] These are at least ten times those reported from North America and Europe.[6, 7] The burden of this disease disproportionately falls on people from poor rural settings, particularly in Africa and Asia.[1] Much of this blindness is avoidable but once established it is difficult to treat.

Most patients have delayed presentations, which contributes to the severity of their disease.[8-10] In addition, our impression has been that although some may have received treatment at a primary health facility, this is often of limited benefit (narrow-spectrum antibiotics) and may sometimes be harmful (topical steroids). In several tropical countries fungal infections (particularly filamentous) have been found to be the causative organism in a large proportion of cases.[8, 11, 12].The management of fungal keratitis remains a significant clinical challenge, as it often penetrates deeply, drugs may be of limited efficacy and prolonged treatment is needed to prevent recurrence.

African population based survey data on the prevalence of blinding corneal opacification attributable to MK indicates that it is a significant ophthalmic public health problem, which receives relatively little programmatic attention compared to other causes of blindness.[14, 15] Moreover, given the severity of this problem, in contrast to South Asia, there are surprisingly few reports on the microbiology, clinical management and particularly the outcomes of microbial keratitis in Africa.[10-12, 16-18] The purpose of this retrospective study was to audit the management and outcomes of patients admitted to Kilimanjaro Christian Medical Centre (KCMC) over a two-year period. Additionally, half-way through this period we introduced a management protocol for

the admitting doctors, which we wanted to evaluate. The protocol specified clinical information to be recorded, microbiology specimens to be collected and initial empirical treatment to be prescribed. Finally, as laboratory diagnostic capacity in many African ophthalmic units is limited to microscopy at best, we report the microbiology results to contribute to treatment guidelines in our region.

Materials and Methods:

This research followed the tenants of the Declaration of Helsinki. It is a retrospective chart review of all individuals admitted to KCMC with microbial keratitis between the 1st January 2008 and 31st March 2010. It was therefore considered by the KCMC Ethics Committee to constitute clinical audit as part of good clinical practice and therefore did not require formal ethics review. Microbial keratitis was defined as ulceration of the corneal epithelium in association with underlying stromal infiltrate. Potential cases were identified from the ward admission register, where the principle diagnosis was recorded. Records were reviewed to confirm whether the individual was admitted for the management of microbial keratitis. Data were collected on the following: demographic information, clinical history, treatment prior to admission, the admission examination, microbiology, treatment during admission and outcome.

In February 2009 the department introduced a protocol for managing severe microbial keratitis. This study afforded the opportunity to evaluate the implementation of this protocol and assess its contribution to the management of these patients. Under this protocol the admitting clinician was expected to collect corneal scraping specimens, which were smeared on a glass slide for gram staining and inoculated onto Blood Agar and Sabouraud Agar plates. Blood and Sabouraud agar plates were incubated for 48 hours and 1 week, respectively. Organisms were identified using standard microbiological techniques. According to the protocol, patients were to be initially given intensive empirical anti-bacterial (g-ciprofloxacin hourly) and anti-fungal (g-econazole hourly) therapy.

Data were entered into a MS Access database and analysed in STATA 11. The time from onset of symptoms to presentation was highly skewed; therefore the Wilcoxon rank-sum test was used to compare the difference in this period between those who came direct to KCMC and those who visited other health facilities first.

Results:

Patient Characteristics:

There were 170 individuals admitted for the management of microbial keratitis between the 1st January 2008 and 31st March 2010; 71 presented before and 99 presented after the introduction of the management protocol. We were able to retrieve the notes for all cases. There were 92 (54%) males. The median age was 46 years (Interquartile Range 25-59 years, Total Range 1-92 years).

Clinical History:

The time between onset of symptoms and presentation at KCMC was skewed: mean 30.0 days, median 14 days, interquartile range 7-30 days, total range 1-365 days. For 13 patients the duration of symptoms was unknown. Ocular injury was reported in 41 (24%) cases. Prior to presenting at KCMC 102 (60%) individuals had visited another health facility. Referrals came from 32 different hospitals and clinics across Northern Tanzania; all were within one day's travel of KCMC. Visiting another health facility was associated with increased time between onset of symptoms and presentation at KCMC: the median time for a direct presentation to KCMC was 8 days compared to 21 days via another health facility (Wilcoxon rank-sum test p=0.0029).

Ninety-two people had received one or more identifiable treatments prior to admission: chloramphenicol (49), ciprofloxacin (18), tetracycline (9), gentamicin (15), povidone Iodine (12) and econazole (4). Twenty-nine (17.1%) people reported topical steroid treatment. Seven people (4%) reported using traditional medicine. Overall, 33 (19.4%) had received a broad-spectrum antibiotic (ciprofloxacin, gentamicin), 59 (34.7%) had received probably ineffective treatment (chloramphenicol, tetracycline, povidone iodine), 40 (23.5%) had received no treatment and for 38 (22.4%) there was no information in the notes.

Examination at Admission:

The uncorrected visual acuity at admission is shown in Table 1. The single largest diameter of the corneal lesion was determined in 145 eyes. Generally these were quite large, with an average diameter of 5.3mm (95%CI 4.9-5.7); 60 (41%) were >5mm in size. A hypopyon was present in 63 (37%) eyes. Corneal perforation was found in 32 (19%) eyes on admission. Presumed microbial keratitis (ulceration with

infiltration) was associated with other underlying pathology in 10 patients (5.9%): Stevens Johnson Syndrome (2), Herpes Zoster Ophthalmicus (2), Moorens Ulcer (3), Rheumatoid arthritis (1) and trachomatous trichiasis (2).

Investigations:

Corneal scrapings were collected from 74 (43%) eyes. Of these, a microbiology result (culture and/or gram stain) was available on only 63 specimens. Organisms were seen on 14/38 (37%) gram stain examinations and cultures were positive in 31/57 (54%), Table 2. Filamentary fungi (moulds) were cultured and/or detected by gram stain in 18/35 (51%) of specimens with a positive microbiology result. Prior to the introduction of the protocol, corneal scraping was performed on 4/71 (5.6%) samples. After the introduction of the protocol, 70/99 (70.7%) were sampled. Five patients reported they were HIV positive at admission. More recently we found that a disproportionate number of patients appeared to be HIV positive. Therefore, our practice is now to routinely offer HIV counselling and testing to individuals admitted with microbial keratitis. Of the 61 individuals tested, 10 (16%) were seropositive positive. These people were referred to the HIV treatment programme at KCMC for assessment and commencement of antiretroviral therapy if indicated. Only 1/15 (7%) of the HIV-positive patients had a history of ocular injury prior to the onset of their MK.

Treatment:

Initial anti-bacterial treatment on admission was with intensive topical ciprofloxacin; this was prescribed in 99% of cases. Anti-fungal treatment was used less consistently as part of initial therapy: prior to the introduction of the treatment protocol 66% received topical econazole or natamycin at least 2 hourly and after the introduction of the protocol this increased significantly to 87% (OR 3.4, 95%CI 1.6-7.2, p=0.002). Tarsorraphy was performed for poorly healing ulcers in 33/170 (19%) of eyes. We do not have access to corneal graft material; therefore, perforations were managed conservatively. Small perforations usually healed well as the infection was brought under control. Larger perforations usually occurred in eyes with severe and extensive corneal necrosis at presentation, and it was often necessary to eviscerate the eye in such cases.

Outcomes:

Healing of the epithelium was observed in 140/166 (82%) eyes (4 eyes missing data). There was a non-significant trend to increased healing after the introduction of the protocol (88% v 75%). In addition to the 32/170 (19%) eyes with corneal perforation at presentation, a further 19/170 (11%) eyes developed perforations during the admission (Total 51 eyes, 30%). The development of a perforation either before or during admission was associated: (i) larger lesions (>5mm) at presentation and (ii) with having visited another health facility prior to presentation at KCMC (Table 3). There was no difference in the post-admission perforation rate before and after the introduction of the protocol.

Evisceration was necessary in 14/170 (8%) eyes. Evisceration was offered but declined in several other cases. The need for evisceration was strongly associated with larger lesions (infiltrate >5mm) at presentation (OR 23.2, 95%CI 2.95-183, p=0.003). No other factors were associated with evisceration. There was no difference in the proportion requiring evisceration before and after the introduction of the protocol.

The final follow-up visual acuity measurements are shown in Table 1. At admission 30/159 (19%) had a visual acuity of 6/60 or better. At follow-up there was a slight improvement with 44/133 (33%) having vision of 6/60 or better. The dominant risk factor for having a blind eye (defined as a visual acuity of less than 6/60) was the size of the lesion at presentation (Table 4). There was a non-significant trend towards a delay in presentation of more than 5 days leading to a worse outcome in vision.

Discussion:

In this study, cases of microbial keratitis were generally severe and had a poor outcome: at discharge 66% were blind in the affected eye, 30% had developed corneal perforations and 8% underwent evisceration. There is very limited published information on the outcomes of MK in Africa to compare our data with.[17, 19] There is undoubtedly a degree of selection bias in favour of more severe cases in our case mix; KCMC is the major referral centre for Northern Tanzania and often the option of last resort. However, despite this caveat, our impression from other ophthalmic units is that our workload is not particularly atypical. Microbial keratitis is a common and frequently blinding problem in sub-Saharan Africa.[1, 14]

The size of the corneal lesion at presentation was a strong indicator of the subsequent clinical course. Having a lesion of greater than 5mm at presentation was associated with the development of a corneal perforation (before or after admission) and a final visual acuity of <6/60. More often than not the patients present too late for the clinician to have much effect on the final functional outcome; extensive corneal damage has already developed.

Several factors may contribute to the severity of disease seen at admission and the poor final outcome. However, what was particularly striking was the long delay between the onset of symptoms and when the patient first received appropriate treatment with intensive antibiotic and/or antifungal therapy. Similar delays have been reported from elsewhere.[8-10] We found that visiting another health facility significantly increased the time between the onset of symptoms and when the patient presented at KCMC. Worryingly, attending another facility was associated with increased risk of perforation, even after adjusting for the size of the lesion at presentation. However, it is possible that more severe cases are more likely to be referred from the other facilities, which might be more likely to have worse outcomes. A recent report from KCMC has examined the reasons for delay in patients accessing specialist care following eye trauma.[20] This study found a mean delay of 6.8 days and a median of 3 days in patients arriving at KCMC after sustaining an ocular injury. This is somewhat shorter then the delay we found for MK in the same population, perhaps reflecting the more abrupt and shocking onset of traumatic problems compared to MK, which may be more insidious. The trauma study identified multiple reasons for delay: significant associations were found with injury during a weekend, using topical treatment before arriving at KCMC and visiting other health facilities.

The authors made several practical recommendations, which apply equally to the problem of MK.[20] These included: development of clear referral systems, empowerment of clinical staff to make referrals too the most appropriate centre, and provision of clear information to the patient about the urgency of the problem.

The prescribing patterns before referral to KCMC were often inadequate or inappropriate. Prior to admission at KCMC only a minority (19%) of patients were known to have received treatment with an appropriate broad-spectrum antibiotic and very few had received an anti-fungal agent. Of the people that had received any treatment, 64% of this was inadequate. Thus in most patients the infection was unchecked for several weeks, allowing deep and extensive lesions to develop. Taken together these observations suggest that there is a major need to review and strengthen training and supervision of primary and secondary level services in relation to the recognition, management and appropriate referral of microbial keratitis.

Filamentous fungi accounted for around half of all culture positive cases. This is consistent with several other studies from tropical regions within Africa.[11, 16, 18] On the basis of these earlier observations we included a topical anti-fungal agent (econazole or natamycin) in our empirical treatment protocol for severe MK. Intensive treatment is maintained until the epithelium heals. We usually continue to prescribe anti-fungal treatment in cases where the clinical features are suggestive of mycotic infection, even if the microbiology result proves negative.[21] Currently, ophthalmic anti-fungal medication is not available in Tanzania outside a few centres, which have to specifically import this medication. Our impression from colleagues in other countries in the region is that limited availability of anti-fungal treatment is a widespread problem. This is a major limitation in the management of microbial keratitis given the high proportion of fungal infections seen; anti-bacterial agents have very limited efficacy against fungal infection.[22] Better access to anti-fungal treatment needed; the inclusion of topical econazole or natamycin on the Essential Drugs lists of countries in this region would be a first and necessary step in improving their availability.

The prevalence of HIV infection (16%) in the MK cases who were tested was more than twice that reported for the adult population in Tanzania (6.5%).[23] This observation is suggestive of increased susceptibility to MK amongst HIV-positive individuals. In addition, the proportion of HIV-positive patients who had a history of ocular injury was low (7%), suggesting a more spontaneous onset. Although offering HIV testing has become our routine practice, it is possible that there could have been some selection bias initially in terms of who was

offered a test. There is no data from Africa on the relationship between HIV and susceptibility to microbial keratitis. A recent population based report from California suggests that the incidence of ulcerative keratitis in HIV-positive individuals is about ten times that occurring in HIV-negative individuals.[24] We found no association between the type of corneal infection and HIV, although a previous study from Tanzania found cases of fungal keratitis were more likely to be HIV-positive than cases of bacterial keratitis.[12] It is important to better characterise the role that HIV may play in MK in this setting. Given the increasing availability of antiretroviral treatment in Africa and the much-improved outlook for patients on treatment, we would suggest that ophthalmologists should routinely offer to put patients with MK in contact with HIV testing services.

Most (82%) cases healed on the empirical treatment schedule. Perforation can be a particularly difficult issue in this environment. Our post admission perforation rate (14%) is similar to that observed in a recent study of fungal keratitis in India (16%).[25] Small perforations were managed conservatively, usually plugged with iris and healed well. For larger perforations our treatment options are limited (conjunctival flaps). In the absence of graft material the eye is often lost. Currently, very few units in sub-Saharan Africa have access to donated corneas for graft surgery. We eviscerated 8% of the admitted cases. There is very little data on frequency of evisceration in MK cases in Africa. One previous report of 44 patients from KCMC found 25% required evisceration.[18] These high evisceration rates reflect the often very advanced stage of the infection at presentation, although it is possible that a therapeutic keratoplasty may have salvaged the eye in a few cases.

To reduce corneal blindness caused by microbial keratitis the emphasis needs to be on prevention and early management. The maxim “prevention is better than cure” is very pertinent. Surprisingly, in our study only about one quarter of people reported an injury to the eye such as a minor abrasion. This is lower than studies from elsewhere: Ghana 39%, Nepal 53%, India 54%.[8, 9, 16] Health promotion messages about eye protection in the work place are important. Moreover, several studies in Asia have now demonstrated that prompt prophylactic treatment of corneal abrasions with topical chloramphenicol is very effective in preventing the development of microbial keratitis.[5, 26] However, this is probably not widely practiced in this region.

The introduction of a management protocol was helpful. Firstly, many more patients had microbiology samples collected, which was often helpful in guiding subsequent management decisions. Secondly, a greater proportion of cases received intensive anti-fungal treatment in addition to the antibiotic, which was prescribed less consistently prior to the introduction of the protocol. However, until issues related to prevention, recognition, initial treatment and prompt onward referral are addressed it is unlikely that we will witness a reduction in blindness from microbial keratitis in Africa.

Table 1: Visual Acuity at presentation and follow-up

Visual Acuity	Admission		Follow-up	
	N	(%)	N	(%)
6/6	1	(0.6)	4	(3.0)
6/9	6	(3.8)	7	(5.3)
6/12	3	(1.9)	5	(3.8)
6/18	2	(1.3)	9	(6.8)
6/24	2	(1.3)	11	(8.3)
6/36	10	(6.3)	7	(5.3)
6/60	6	(3.8)	1	(0.7)
CF	34	(21.3)	23	(17.3)
HM	46	(28.9)	27	(20.3)
POL	43	(27.0)	17	(12.8)
NPL	6	(3.8)	22	(16.5)
Not Recorded	11		37	

CF counting fingers, HM hand motion, POL perception of light, NPL no perception of light.

Table 2: Microbiology Results from gram stain microscopy and culture.

Organism	n	(%)
Gram Stain (n / 38)		
No organisms seen	25	(65.8)
Gram-positive cocci*	1	(2.6)
Gram-negative rods	1	(2.6)
Candida	2	(5.3)
Filamentary Fungi	10	(23.7)
Culture (n / 57)		
No Growth	26	(45.6)
Streptococcus pneumoniae	1	(1.7)
Viridans group *Streptococci*	2	(3.5)
Pseudomonas aeruginosa	3	(5.3)
Staphylococcus epidermidis	8	(14.1)
Bacillus spp.	1	(1.7)
Candida spp.	2	(3.5)
Filamentary fungi	14	(24.6)

*One specimen had both gram-positive cocci and filamentary fungi present on gram staining.

Table 3: Risk factors for corneal perforation before or during admission, univariate associations and a multivariable logistic regression model.

Risk Factor	OR	(95%CI)	P value
Univariate associations			
Infiltrate >5mm at presentation	4.77	(2.26-10.1)	<0.001
Visited other health facility	2.94	(1.40-6.16)	0.004
Effective treatment before admission	0.90	(0.38-2.11)	0.802
Sex (male)	1.83	(0.93-3.61)	0.080
Delay in presentation >5 days	2.41	(0.86-6.77)	0.095
Multivariable logistic regression model			
Infiltrate >5mm at presentation	4.68	(2.19-10.0)	<0.001
Visited other health facility	2.51	(1.10-5.77)	0.030

Table 4: Risk factors for a blind eye* at final follow-up, univariate associations and a multivariable logistic regression model.

Risk Factor	OR	(95%CI)	P value
Univariate associations			
Infiltrate >5mm at presentation	11.38	(3.66-35.4)	<0.001
Corneal perforation before or during admission	3.83	(1.54-9.55)	0.004
Visited other health facility	0.92	(0.44-1.95)	0.837
Effective treatment before admission	0.41	(0.17-0.99)	0.048
Sex (male)	1.12	(0.54-2.31)	0.763
Delay in presentation >5 days	3.29	(1.27-8.49)	0.014
Multivariable logistic regression model			
Infiltrate >5mm at presentation	7.68	(2.35-25.1)	0.001
Delay in presentation >5 days	2.61	(0.84-8.13)	0.098
Corneal perforation	1.99	(0.65-6.06)	0.229

*Blind eye defined as visual acuity less than 6/60.

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